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TITLE: Applying Statistical Models to Mammographic Screening Data to Understand Growth and Progression of Ductal Carcinoma in Situ

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14. ABSTRACT
Little is known about the natural history of ductal carcinoma in-situ (DCIS). Estimates from studies of recurrence following surgery suggest about 30% recur as invasive cancer. The aim of this study is to use novel applications of statistical methods to estimate the proportion of DCIS that progress to invasive cancer. We first analysed observed screening data and showed that neither time since previous negative screen or HRT use were associated with size of DCIS. Similar results were found for histological grade. We have developed a computer simulation for mammographic screening data which models progression and detection of Ductal carcinoma in situ. Based on various options for growth, detection and invasion, we have simulated various distributions of DCIS sizes for a screening program. These distributions can then be used to test hypotheses regarding different scenarios of growth and invasion of DCIS. Our preliminary results to date show that low growth rates and low invasion rates provide the best fit to the data. Further work will include the addition of screening round and different mechanisms of invasion to the modeling. We are presently validating our findings on an independent data set.

15. SUBJECT TERMS
Mammographic screening, DCIS, statistical models

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INTRODUCTION

Little is known about natural history and growth patterns of DCIS. It is estimated that about 30% of DCIS may progress to invasive cancer[1,2,3], based on studies of long-term follow-up of DCIS initially mis-diagnosed as benign, but this cannot be studied directly. Previous models of invasive tumor growth have used the distribution of tumor size (as measured by diameter) at detection and assumed constant growth[4,5]. These models are parameterised by tumor volume; however, these assumptions may not hold for DCIS. The aim of this proposal is to apply novel statistical models to explore the growth patterns of DCIS. Our approach differs from previous models in that we model the DCIS phase (both growth and invasion) and model detection via mammography at discrete intervals. These models may lead to new insights into natural history of DCIS that can be used to predict DCIS growth and may provide important data for clinical management.

BODY

Substantial progress has been made in modeling and simulation of growth of DCIS, in particular for Tasks 2 and 3. We were successful in obtaining additional funding for this work (NHMRC Postdoctoral fellowship) and thus the research is still ongoing, as we are now validating the findings on an independent data set. Below we describe the progress on each task related to the statement of work. **All data presented are preliminary.**

Task 1:

Validation of measures of DCIS size, comparing reported size on pathology reports with size as measured on mammograms.

Progress on this aspect of the study was delayed due to difficulty in finding a radiologist associated with the program who has the time commitments to conduct measurements of DCIS size on mammograms in the validation study. We are about to commence this work in collaboration with a pathologist at St Vincents hospital in Melbourne.

Tasks 2 and 3: The progress on Tasks 2 and 3 is described together as they are inherently linked to the modeling and simulation of DCIS growth rates.

Preparation of data set:
We received de-identified data from BreastScreen Victoria (BSV), a free mammographic service to Victorian women aged 50-69 years, every two years, with the aim to reduce breast cancer mortality. The program was established in 1992 and currently screens about 160,000 women each year. Participation is approximately 58% of all eligible Victorian women between 50-69 years of age. In this study we used data routinely collected by BSV including information on age, hormone replacement therapy (HRT), family history, symptomatic status, and date of each screen in addition to tumor characteristics: histopathology, tumor size (mm) and histological grade and whether diagnosis was DCIS or invasive cancer.

Data management and coding of relevant variables were conducted using Microsoft ACCESS and STATA. Key variables of interest were time since previous negative screen coded as the time in months from most recent screen (prior to diagnosis) to the previous screen. HRT was coded as HRT use at most recent screen (yes, no) and years of HRT use at most recent screen (None, 1 to 5 years, over 5 years). Age at diagnosis was coded in years. Histological grading is defined as grade 1: Low grade (well differentiated), grade 2: Intermediate grade (moderately differentiated) and grade 3: High grade (poorly differentiated) and unknown grade.

Background work:
i. Review of literature on natural history of DCIS

Prior to commencing the work on simulation and modeling of DCIS, we reviewed the literature on evidence regarding the natural history of DCIS and in particular modeling relevant to the natural history. A manuscript is about to be submitted to the journal Cancer (see reportable outcomes). The available evidence suggests that only a modest proportion of DCIS may progress to invasive cancer; however, all sources of evidence have limitations that may bias the estimates in either direction.

ii. Preliminary analyses characterizing DCIS size and grade in relation to screening interval. To characterize DCIS size distributions for women attending a subsequent screen we used multiple linear regression methods. The models comprise of an age adjusted base model with each predictor entered in a step-wise manner with exclusion criteria based on the p value for each likelihood ratio test. To investigate associations between HRT use at diagnosis screen and size, the data was stratified by women aged over 55 years. Multinomial regression methods were used to evaluate predictors of histological grade. These methods are extensions of logistic regression where the outcome consists of more than two categories (histological grade consists of three levels; high, intermediate and low grade). Potential predictors of grade were entered into the model in a similar fashion to the predictors of size. All analyses were completed using the statistical package STATA version 7.

In BreastScreen Victoria n = 1127 women were diagnosed with non-invasive breast malignancy – n = 552 Comedo, n = 319 non-comedo, n = 228 mixed and n = 28 other DCIS between 1993 and 2000. Of these, n=590 were diagnosed at the first screen and n=537 were diagnosed at repeat screen. Of the DCIS diagnosis n = 724 women had non-missing tumor size (mm). Table 1 shows results of a multivariate regression of predictors of log-transformed size. Only high grade ($p < 0.001$) was associated with larger lesions. When restricted to subsequent attendees of the program a longer screening interval was not associated with size. Neither HRT use, nor duration of HRT use was associated with DCIS size. Multinomial regression models were constructed to assess the multivariate effects of country of birth, area of residence, symptomatic status, previous benign breast disease, histology, grade, family history, and HRT status on histological grade adjusting for age at diagnosis (Table 2). High grade lesions were 6 times more likely to be larger (> 20mm) in comparison to low grade lesions, $p < 0.001$ (95% CI 2.3 to 15.73). For subsequent attendees of the program time since previous negative screen (months) was not associated with an increased risk of high grade tumors ($p = 0.2$).

These preliminary results suggest that DCIS is relatively slow growing, at least within relatively short screening intervals of several years, as time since screen does not predict size of DCIS. However, an important issue is at what size DCIS is likely to invade and whether this depends solely on size of the tumor.

iii. Simulation and modeling of growth rates of DCIS using BreastScreen data.

Previously we had planned to use the simulation in the following way:

a. Simulate size of DCIS at first and subsequent screen under various scenarios of tumour initiation, growth, detection
b. Compare simulated distributions to data from screening program (BSV)
c. Identify scenarios that are compatible or not with BSV data

However, in the last 12 months our methodology has improved greatly, to the point where instead of only being able to determine if a given scenario is compatible or not with the BSV data, we are now able to use the simulation to identify the 'best' scenario of growth and invasion. We now use a maximum likelihood approach which we hope will not only give parameter estimates by also standard errors for these estimates.

The likelihood is maximised for the scenario with a median growth rate of 1.1 mm/year and a median size at invasion of 6mm. The log-likelihood surface which gave rise to these estimates is plotted in Figure 1, below.

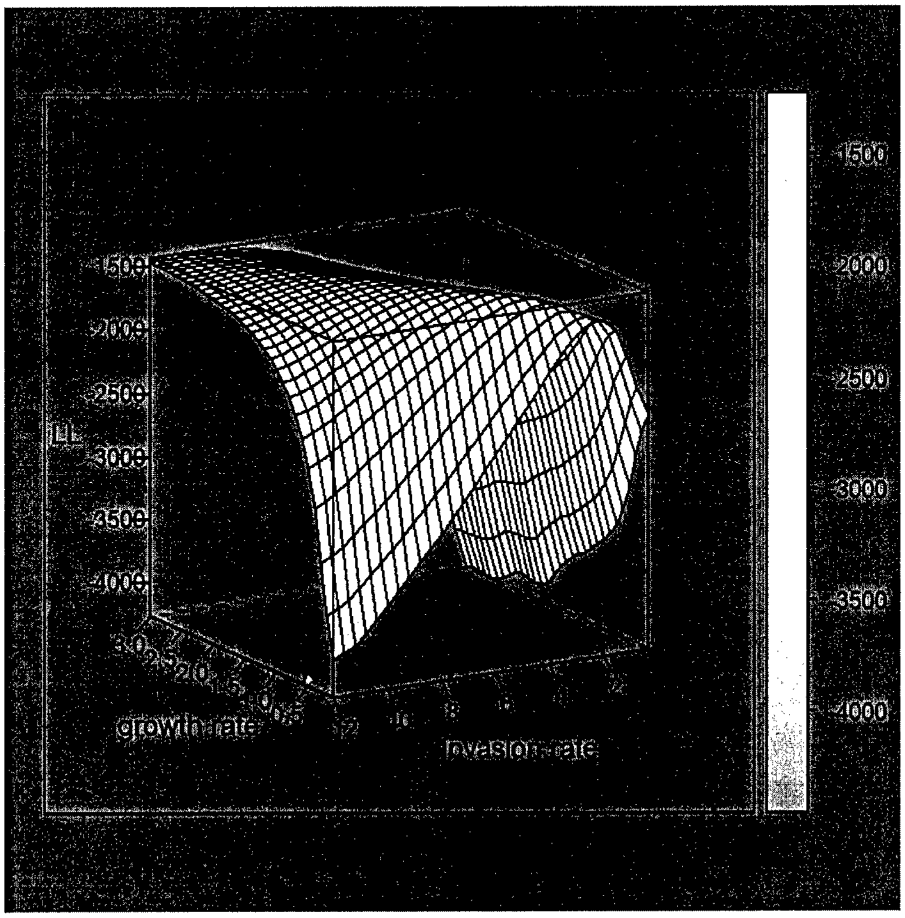


Figure 1

As decribed in our last report, the simulation has been implemented in C++ and an executable version is available for the Windows Xp platform. However since the source code is also available the program can be run on any computer with a C++ compiler. The simulation begins with various menus and prompts asking the user to enter details such as the name of the output file and the number of subjects to simulate. The user is also asked to choose from various options related to tumor initiation, growth and detection.

The flowchart below (Figure 2) depicts the simulation's control flow for each subject. The program iterates until it has generated the required number of subjects with a detected tumor.

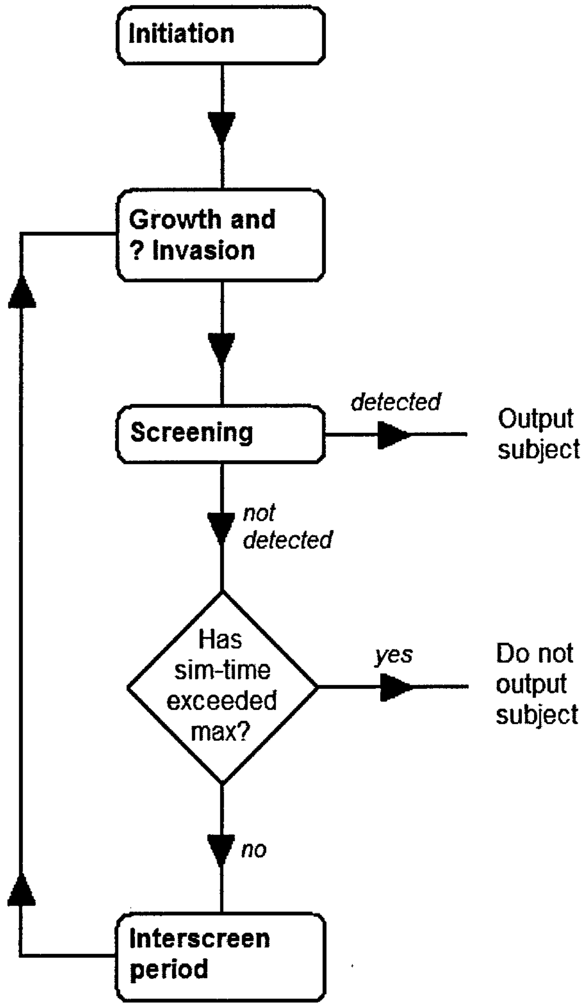


Figure 2

For each subject, the simulation begins by randomly choosing the subject's age at tumorigenesis and at first screen. Age at tumorigenesis is selected from the distribution which Pike *et al*[6] suggest for the incidence of breast cancer, though we estimate key hormonal risk factors such as the distribution of ages at menarche from the control group of the Australian Breast Cancer Family Study[7]. Age at first screen is chosen from a uniform distribution with range 45 to 75 years. This approximates the distribution observed in the BreastScreen Victoria mammography data collected between 1993 and 2000[8].

Next a grade is assigned to the tumor according to a set of probabilities chosen by the user. Growth rates for DCIS and IBC are drawn from grade-specific distributions. If the user has chosen the logistic growth option then a limiting size is also randomly selected. The size of the tumor is set to a starting value, usually the size of one cell. Each tumor starts as DCIS.

In the first instance, growth and potential invasion are simulated for the period of time from tumor initiation to first screen (unless tumorigenesis occurs after the first screen, as discussed above). After this, growth and potential invasion are simulated for the periods of time between consecutive screenings.

The growth module simulates a period of growth by updating the size of the tumor. Growth is simulated for both DCIS and IBC or just for DCIS, depending on whether invasion has occurred or not. The simulated growth depends on the length of the growth period, the rate of growth, the

type of growth (exponential, linear, logistic or power law) and a limiting size if logistic growth has been selected. We also plan to use back-calculation techniques to determine the proportion of invasive breast cancers that arise from DCIS.

iv. Analytic modeling of DCIS and comparison to BreastScreen data.

The modeling work is near completion and is awaiting the availability of a secondary data source to validate findings. This work is complementary to the simulation work described above, in that it helps identify those parameters which are most important in adjusting the models to fit the observed data. Of equal importance is the ability to recognise that some parameters may not be "identifiable", which is to say they cannot be estimated from data of this type regardless of quantity or quality.

We considered a total of nine models, being all combinations of three growth models and three invasion models. The growth models were

1. Constant rate of growth (linear increase of size with time);
2. Constant rate of doubling (exponential dependence of size on time);
3. Decreasing rate of growth with size (Gompertz model).

These were chosen as exemplars three broad families of models. The first represents those where the growth is dependent on the supply of nutrients. While constrained to the ducts, this implies a constant growth rate since nutrients can only be absorbed at the growing ends of the tumor. The second is a model where nutrients are assumed to be unlimited and the tumor grows as cells duplicate at a constant mitotic rate. The third is a traditional model of solid tumour growth where the mitotic rate decays as the tumor approaches some limiting size.

The invasion models were

1. A hot-spot model where the DCIS penetrates the duct wall as soon as it reaches a pre-existing weak-point;
2. A "Markov weakening" model where the tumour attacks the duct wall with lysing proteins throughout their region of contact. The rate of penetration per unit area is assumed constant, implying an exponential time to penetration at any given point;
3. A progressive weakening model, where the rate of penetration at a given point increases with prolonged contact.

Again, these were chosen as representative models.

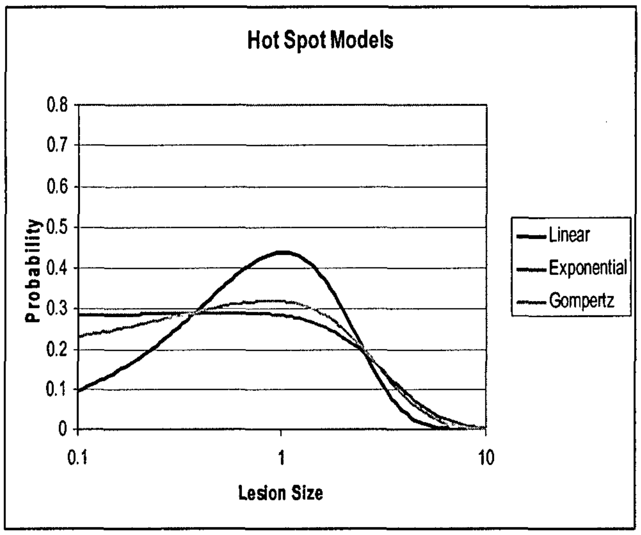
The above models were then combined in a partial differential equation which represented the evolution of the distribution of DCIS tumor size in the population. This allowed for the creation of new DCIS, followed by growth until either detection by screening, development of invasive cancer, or the end of the screening age-range. To simplify interpretation, we have initially supposed that initiation occurs at a constant rate. With this assumption it was possible to exactly solve the above differential equation and predict the functional from of the distribution of detected DCIS sizes for comparison with data.

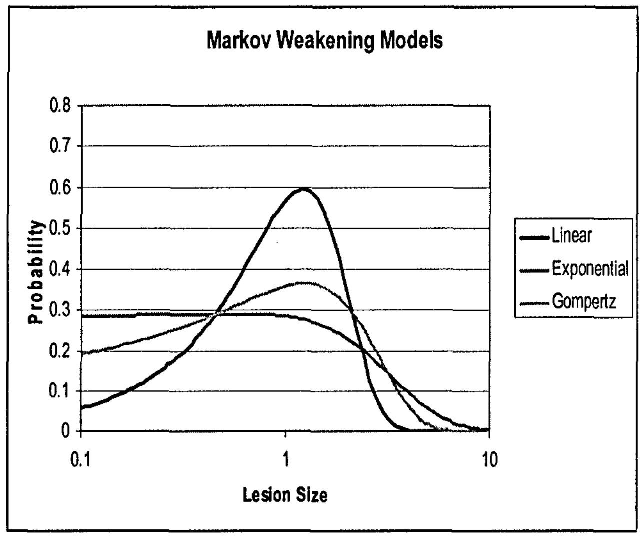
One notable feature was that in all cases the parameter describing the rate of invasion could not be estimated independently of the rate of growth. In fact in the hot-spot model, the predicted distribution is found to be independent of the rate of growth and depends only on the number of weak-spots per unit length of duct. For the other invasion models the predictions depend only on combinations of the growth and invasion rates: their ratio for the Markov weakening model; or the invasion rate divided by the square of the growth rate for the progressive weakening model.

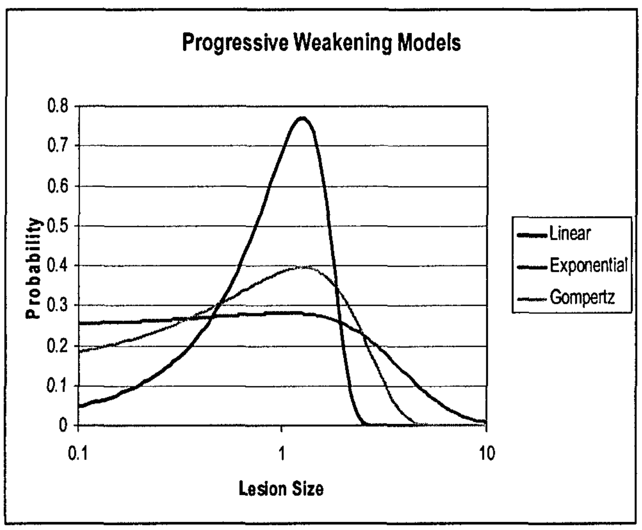
Predicted distributions of log-size are illustrated below, with all means standardized to one to allow comparison of other features. At this stage we have not allowed rates of growth and invasion to vary between women, as it surely does in reality. However, implementing this would amount to convolving the distributions below with the distributions of the appropriate ratios of

parameters. One consequence of our work is that if growth and invasion rates are correlated then they will tend to cancel each other out. In any case the effect will be to broaden the distributions rather than change their fundamental character.

The current data suggest that the linear growth model provides the best fit, while we are less confident about out ability to distinguish invasion models. The progressive weakening model seems the least likely to be correct, although we await additional data before making any final conclusions.







Task 4: Manuscript preparation

We have completed a review of the literature on natural history of DCIS and this has been accepted for publication in Breast Cancer Research and Treatment. Erbas et al "The natural history of Ductal Carcinoma in situ of the breast: a review".

Several other manuscripts are presently in preparation:
Erbas et al "Trends and predictors of size and grade of DCIS within a screening program"

Dowty et al "A comparison of breast cancer invasion mechanisms".

Manuscript preparation is continuing beyond the funding provided by the DOD concept award.

Positive and negative findings

Our findings to date are:

1. Existing evidence from the literature suggests that not all DCIS will progress to invasive cancer; however, all data sources are limited and may potentially bias results in either direction.
2. Size and grade of DCIS are not determined by time since previous screen, suggesting that, at least within moderate screening intervals observed in this program, growth rates of DCIS are likely to be slow.
3. Preliminary results from the simulation of observed DCIS size distributions from a screening program suggest that low growth and low invasion rates are most compatible with the observed data.

Problems in accomplishing tasks and recommended changes

An issue in the modeling work is trying to capture the inherent complexity of the process of growth and invasion. Although our preliminary simulations fit the data quite well, it has proved difficult to adequately simulate the size distribution at subsequent screen. We are exploring the possibility of restricting the models to specific grades of tumors, as it is possible that the simulations may require stratification by tumor grade, which is a known determinant of tumor growth rates. Our results are presently being validated in another data set from a screening program.

KEY RESEARCH ACCOMPLISHMENTS/FINDINGS

1. We have reviewed the literature on natural history of DCIS (manuscript accepted for publication). The data suggest that not all DCIS progress to invasive cancer and show that all sources are limited and may bias estimates in either direction.
2. We have analyzed existing data from the screening program to determine predictors of DCIS size and grade. Our results show that grade is the strongest predictor of size and that time since screen does not predict either DCIS size or grade. HRT use is associated with better grade DCIS (similar to invasive cancer) but is not associated with size of DCIS.
3. We have made significant progress in the modeling and simulation of observed DCIS size distributions from a screening program under different assumptions of growth, invasion and detection. We have developed a maximum likelihood approach to estimate growth and invasion rates. This gives a median growth rate of 1.1 mm/year and a median size at invasion of 6mm, though these estimates must be treated with some caution since they do not come with standard errors and are presently being validated in an independent data set.

REPORTABLE OUTCOMES

Manuscripts:

Erbas B, Provenzano E, Armes J, Gertig DM The natural history of DCIS of the breast: a review. To be submitted to Cancer 9/04.

Erbas et al Trends and predictors of size and grade of DCIS within a screening program. (in preparation)

Dowty et al A comparison of breast cancer invasion mechanisms. (In preparation)

Byrnes et al Simulation of DCIS detection and invasion: comparison with screening data (In preparation)

Published Conference Proceedings/Abstracts

Erbas B., Chang J-H., Byrnes G., Provenzano E., Kavanagh AK., Gertig DM. Trends and predictors of size and grade for Ductal Carcinoma In Situ diagnosed within a mammographic screening program. (*Proceedings from the Symposium Mammographicum July 2004)*

Erbas B., Chang P., Byrnes G., Provenzano E., Kavanagh AK., Gertig DM. Trends and predictors of size and grade for Ductal Carcinoma In Situ diagnosed within a mammographic screening program. (*Proceedings from the Australasian Epidemiological Association October 2004)*

J. Dowty et al., Investigating the natural history of DCIS using a computer-based simulation *(Proceedings from the Australasian Epidemiological Association October 2004)*

J. Dowty et al Investigating the natural history of DCIS using a computer-based simulation. Presented at DOD Era of Hope meeting 2005.

Awards

"Natural history of Ductal carcinoma in situ of the breast: using statistical models to estimate growth and progression". Faculty of Medicine, Dentistry & Health Sciences Annie S Glover Research Fellow Award in Cancer (PI: Bircan Erbas).

"Novel Applications of Statistical Methods to Breast Cancer Data". National Health Medical Research Council Australian postdoctoral fellowship (PI: Bircan Erbas)

LIST OF PERSONNEL RECEIVING PAY

Dr Bircan Erbas (Post-doctoral fellow)

Ms Annette Fedson (Research assistant)

Dr James Dowty (Statistician)

Dr Dorota Gertig (Senior Research Fellow)

CONCLUSIONS

New approaches to estimate the natural history of DCIS are essential. The aim of this study is to use novel applications of statistical methods to estimate the proportion of DCIS that progress to invasive cancer. We have developed a computer simulation for mammographic screening data which models progression and detection of Ductal carcinoma in situ. Based on various options for growth, detection and invasion, we have simulated various distributions of DCIS sizes for a screening program. These distributions can then be used to test hypotheses

regarding different scenarios of growth and invasion of DCIS. Our results to date show that low growth rates and low invasion rates provide the best fit to the data. Further work will include the addition of screening round and different mechanisms of invasion to the modeling. We are presently validating our findings on an independent data set from a mammographic screening.

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APPENDIX 1: Predictors of size and grade of DCIS. Results from preliminary analyses of existing BreastScreen data.

Table 1: Results of multivariate regressions analysis of log size and HRT use and various risk factors adjusting for age at diagnosis for screen-detected DCIS within BreastScreen Victoria

	Variables	Beta coeff. Estimate #	s.e. #	95% CI #	P value#
	Age				
	50-69 yrs	--	--	--	--
	< 50 yrs	0.29	0.15	(-0.01, 0.60)	0.06
	> 69 yrs	-0.07	0.13	(-0.32, 0.18)	0.59
	Country of birth				
	Australasian	--	--	--	--
	UK	0.12	0.16	(-0.18, 0.43)	0.43
	Europe	0.13	0.13	(-0.13, 0.38)	0.32
	Asian	-0.09	0.20	(-0.49, 0.31)	0.66
	Other	-0.03	0.24	(-0.49, 0.43)	0.90
	Symptoms				
	No	--	--	--	--
	Ever	-0.20	0.18	(-0.55, 0.15)	0.27
	Postcode				
	Capital city/ major urban	--	--	--	--
	Rural/remote	-0.11	0.13	(-0.36, 0.14)	0.39
	Previous breast disease				
	No	--	--	--	--
	Ever	0.02	0.10	(-0.18, 0.22)	0.83
	Histology				
	Comedo	--	--	--	--
	Non-comedo	-0.14	0.15	(-0.43, 0.16)	0.37
	Mixed	0.07	0.13	(-0.17, 0.32)	0.56
	Other	0.03	0.27	(-0.50, 0.57)	0.90
	Grade				
	Low	--	--	--	--
	Medium	0.43	0.15	(0.13, 0.73)	0.005
	High	0.75	0.17	(0.42, 1.08)	<0.001
	Family history				
	First degree	--	--	--	--
	Second degree	0.04	0.22	(-0.40, 0.48)	0.85
	Unknown/other	0.21	0.20	(-0.19, 0.61)	0.30
	Time since last negative screen **	0.01	0.01	(-0.02, 0.04)	0.42
Age >=55yrs	**HRT use**				
	No	--	--	--	--
	Ever	0.19	0.14	(-0.09, 0.46)	0.18
	HRT duration				
	None	--	--	--	--
	1-5 yrs	0.24	0.23	(-0.21, 0.70)	0.30
	> 5 yrs	0.16	0.16	(-0.15, 0.48)	0.31
	Time since last negative screen **	0.02	0.02	(-0.02, 0.06)	0.41

Table 2: Results of multinomial regression of histological grade and various risk factors adjusting for age at diagnosis for screen-detected DCIS within BreastScreen Victoria

		Grade 3 vs 1		Grade 2 vs 1	
	Variables	**OR (95% CI) #**	**P value**	**OR (95% CI) #**	**P value**
ALL WOMEN:					
	Age				
	50-69 yrs	--	--	--	--
	< 50 yrs	0.83 (0.25, 2.72)	0.76	0.74 (0.26, 2.10)	0.57
	> 69 yrs	1.01 (0.39, 2.62)	0.99	1.17 (0.50, 2.73)	0.71
	Country of birth				
	Australasian	--	--	--	--
	UK	1.02 (0.29, 3.56)	0.97	0.61 (0.19, 1.94)	0.40
	Europe	1.27 (0.45, 3.54)	0.65	1.09 (0.42, 2.80)	0.86
	Asian	1.64 (0.33, 8.12)	0.54	1.53 (0.39, 6.01)	0.54
	Other	2.63 (0.32, 21.80)	0.37	2.25 (0.33, 15.38)	0.41
	Symptoms				
	No	--	--	--	--
	Ever	1.62 (0.40, 6.55)	0.50	1.56 (0.44, 5.49)	0.49
	Postcode				
	Capital city/ major urban	--	--	--	--
	Rural/remote	1.64 (0.57, 4.74)	0.36	1.1 (0.40, 3.09)	0.84
	Previous breast disease				
	No	--	--	--	--
	Ever	0.70 (0.33, 1.52)	0.37	0.68 (0.34, 1.38)	0.29
	Histology				
	Comedo	--	--	--	--
	Non-comedo	0.004 (0.001, 0.01)	<0.001	0.09 (0.03, 0.23)	<0.001
	Mixed	0.29 (0.08, 1.01)	0.05	0.82 (0.22, 2.98)	0.176
	Other	0.03 (0.007, 0.14)	<0.001	0.10 (0.02, 0.48)	0.004
	Size				
	< 10 mm	--	--	--	--
	10-20 mm	2.14 (0.90, 5.06)	0.08	1.20 (0.53, 2.71)	0.66
	> 20 mm	6.02 (2.30, 15.73)	<0.001	3.34 (1.38, 8.08)	0.007
	Family history				
	First degree	--	--	--	--
	Second degree	1.09 (0.21, 5.58)	0.92	2.52 (0.54, 11.82)	0.24
	Unknown/other	1.55 (0.35, 6.90)	0.57	2.11 (0.50, 8.86)	0.31
	Time since last negative screen **	0.98 (0.87, 1.10)	0.73	0.96 (0.85, 1.08)	0.49
Age ≥ 55:					
	HRT use				
	No	--	--	--	--
	Ever	0.48 (0.16, 1.44)	0.19	0.51 (0.18, 1.39)	0.19
	HRT duration				
	None	--	--	--	--
	1-5 yrs	0.40 (0.08, 2.02)	0.27	0.54 (0.14, 2.14)	0.38
	> 5 yrs	0.51 (0.14, 1.91)	0.32	0.48 (0.14, 1.69)	0.26
	Time since last negative screen **	0.87 (0.73, 1.05)	0.14	0.90 (0.76, 1.06)	0.21